CHANGING PATTERNS

an atypical autobiography

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being unjustly treated and began collecting material for a monograph on antibody production which the Institute could publish without risk of veto by editors! A thoroughly immoral attitude, but in one way and another it opened the road that led eventually to Stockholm.

CHAPTER 7

War-time Visit to America

Looking back on the experiences which influenced my development as a professional investigator in infectious disease of man and the field relevant thereto, I must place a lot of importance on the American visit of 1943-44. I have already told of the invitation to Harvard for the Dunham lectures and how I went to America as Director-elect of the Walter and Eliza Hall Institute. It was a critical moment of my career. It was almost inevitable either that I should remain in America or that if I came back to Australia my approach to directing the Institute would be very strongly influenced by experience of the American pattern of research. I did return to Australia deeply impressed and for at least the next ten or twelve years I worked hard to bring medical research in Australia into a form patterned on the American model.

The impression that America made on me was almost overwhelming. By the end of 1943, the early war-time confusion had passed and the whole industrial and intellectual resources of America had swung into action. My friends, interested as they all were in the control of infectious disease, had more work to do and better facilities to do it than ever before. No one doubted that control of infectious disease in the Armed Services was as important medically as the treatment of casualties. I had come with some first-hand knowledge of the scrub typhus and dengue which with malaria were vital factors in the war in New Guinea and onwards. In the laboratories, viral and rickettsial diseases were just becoming susceptible to practical approaches and DDT, the first of the fabulous insecticides, was just off the secret list. Penicillin was at the first stages of commercial production

and the first effective exploitation of human plasma derivatives, gamma globulin, for example, had begun.

I found it easy to identify myself with all these activities. My own influenza work was well known and everyone was eager to hear anything I had to tell and more eager to tell me what they were doing. Everywhere fundamental work was throwing up practical applications and new fundamental work being called for by experience in the field. It is a pattern of activity that has now almost disappeared but it was very real then and it supplied the conscious ideal for the subsequent activities of the Institute in Melbourne. When I came back I put my ideas in order and published them as a call for a combination and revitalization of education and research in Australia on the American model. I shall quote fairly extensively from that lecture but first I should describe at a more personal and specific level some of the incidents and impressions of that war-time visit.

The three weeks' voyage across the Pacific was wholly uneventful until we arrived in San Francisco on 4 December. It was a Saturday morning and the first news we had was thoroughly depressing. There were no hotel beds available in San Francisco, no banks open till Monday and a waiting-list of three weeks before one could get a train berth across the continent. I can quote from a diary letter how I made a friend and solved all those problems together. I had known Dr K. F. Meyer of the Hooper Foundation in San Francisco well by scientific repute and by correspondence when we were both working on psittacosis but I had never met him. He knew I was coming to the States and I had arranged to call on him when I arrived. I reached the Hooper Foundation, and now I quote:

> 'Then Meyer came in and has taken complete charge of me. He is a tremendous personality—I think it highly probable that de Kruif used him as part of the model of Sondelius in *Martin Arrowsmith*. He is a Swiss by birth and a mountain-climber by nature, still has a fairly strong German accent, speaks loudly and forthrightly. He knows everybody, including all the politicians and plutocrats of California, and seems to get on very well with them despite his very liberal views and his burning passion to smoke out plague squirrels and rats and psittacotic birds, completely regardless of vested interests. So, characteristically, he rang the State Health Officer to see that I got a room in the Fairmont and, of course, there was a room just being vacated. Then he booked me a Pullman berth to Chicago and generally mapped out my itinerary for the next month.'

On most occasions when I have visited San Francisco since then, I have seen 'K.F.' and many of our Californian experiences have in some way been associated with him. None of them, however, had quite the impact of my first visit. K.F., as I have indicated, had influence in many quarters and found transport and accommodation for me in a way which made my war-time travels almost easy. Along the way and when I was back in San Francisco waiting for a return passage, I heard many of his stories and was infected by his enthusiasms. I was specially interested in his friendship with Paul de Kruif and his association with Sinclair Lewis' novel, *Arrowsmith*.

Circumstances combined to give me a special interest in that novel. It was published in 1924 and created a stir amongst laboratory people in America. Ripples reached Australia and I was given a copy for shipboard reading when I left for England in July 1925. I enjoyed the story and, being young and fresh from my first dabblings with bacteriophage, which Martin Arrowsmith in the novel had discovered independently of d'Herelle in 1917, I more or less identified myself with the hero. With the inevitable result that when I took the plunge and acquired a fiancée in October 1926, Linda in her turn was given the book for shipboard reading on the way back to Australia.

That sentimental attachment to the novel was re-awakened when Meyer told me how he and de Kruif had first discussed the possibilities of a novel dealing with medical research one day when they had climbed to the top of Mount Tamal Pais, a few miles north of San Francisco. It was after that seminal discussion that de Kruif interested Sinclair Lewis in the possibilities and *Arrowsmith* was written.

Arrowsmith deals with the period that saw my first induction into medical research and almost the first contemporary bacteriological paper that I studied in relation to my own research was one by Northropp and de Kruif in the *Journal of Experimental Medicine* of 1923. I saw nothing of de Kruif on this first visit and though my only contact with him came nearly ten years later it had a spice of its own and must be told here. We were in

San Francisco and once again Dr Meyer was looking after us. K.F. told us he had been bidden to dinner by the de Kruifs and had suggested, successfully, that Linda and I should be included in the party. We were to meet for drinks at the Fairmont and in due course found ourselves in a room full of noise and hard liquor. We at home were more accustomed to sherry and Linda murmured that she would like a dry sherry. There was no sherry, of course, and de Kruif reached for the phone. I still remember part of the conversation: 'Yes, sherry . . . sherry! . . . Yes, imported sherry, of course . . . Well, send both!' And two bottles of Spanish sherry arrived to our embarrassment. We had dinner at Trader Vic's—a very pleasant meal in the course of which I learnt that the woman sitting next me (Mrs de Kruif) was the prototype of that most attractive of fictional heroines, Leora of *Arrowsmith*.

In due course I started my three-day journey to Chicago by taking the ferry to Oakland and learning for the first time what a Pullman car was like. In Chicago I spent an hour or two between trains at the municipal VD clinic where there was a crash programme to render all patients with syphilis non-infective in three days. Though we did not know it then, penicillin was just about to take over as the primary means of treating syphilis. In Chicago the treatment was a combination of arsenicals and artificial fever. It was soundly enough based, with the knowledge then available, and had a curious side-effect which at that time was of special interest to me. If any of the patients were carriers of herpes virus, their artificial fever would infallibly induce the appearance of herpes blisters on the lips. One of the main topics I had prepared for the Dunham lectures was the natural history of herpes infection and here was a nice corroboration of the point of view I had adopted and which is briefly outlined in another chapter.

At Washington I caught up with Dr Meyer again and found myself in a whirl of laboratory visits, lectures and dinners. As K.F.'s protegé I seemed to have the entrée everywhere. I talked about typhus with Plotz, about plans for the use of penicillin with Keefer, and learnt many things which are now completely forgotten. Before and after Harvard I travelled extensively, including Ann Arbor, Grand Rapids, New Haven, Cleveland, St Louis, Toronto and Fort Bragg, and when I got back to the West Coast, Los Angeles, Bakersfield and San Francisco. It was

enough to see a wide cross-section of academic life and to absorb something of the general American pattern of life.

Experience as Dunham lecturer of the Harvard Medical School was different from anything that had ever come my way. I was most fortunate that the Faculty had deputed John Enders to look after me. This was the beginning of a friendship that has been strengthened on each of our visits to America. In January 1944, Enders was working with mumps virus, coaxing it to grow in tissue culture. It was the opening phase of the process which led steadily to his success in working out technical methods for growing the virus of polio in tissue cultures of monkey cells. For this, Enders, Robbins and Weller shared a Nobel Prize in 1954 and by the use of Enders' techniques the Salk and Sabin vaccines were developed. The polio vaccines turned out to be quite fantastically successful and for the last six years polio has virtually disappeared from the developed countries of the earth. The major credit for this goes to John Enders.

When I arrived in Harvard, Enders handed me a paper, still in my scrapbook, with three columns for morning, afternoon and evening engagements for each day of the twelve I was spending in Boston. There was only one of the thirty-six spaces unfilled: the Faculty certainly kept me occupied and I appreciated every hour. It was the first time that I had ever had an opportunity to meet on friendly terms with men whom I knew to be great by any standard. At the traditional dinner for the Dunham lecturer, most of the medical faculty were present. On looking over the list twenty-three years later, one recognizes many of the greatest names in American medicine, Aycock, Albright, Aub, Burwell, Castle, Minot, Means, General Russell, E. B. Wilson, Dubos, Enders, Müeller, Wolbach and Wislocki. The following week I was entertained at the Fellows' Club, which I was told had been founded twenty years previously but already had traditions which anywhere else would have taken three hundred years to acquire. I sat next the president, Whitehead, whom I revered as the greatest living philosopher but heard very little from during the course of the meal. On the other side was a young entomologist immensely interested in and articulate about the problems of insect flight. Twenty years later I found Carol Williams, now head of the Biology School at Harvard, talking just as enthusiastically about 'juvenile hormone' and the other hormones which play such an extensive part in the development of insects.

Characteristically he had just made one of those 'silly' discoveries which, when they occur, fill everyone with delight. In one phase of his work on insect development it was convenient to use old newspaper for some apparently trivial purpose. Eventually it emerged that the newspaper was doing something really important. If *The New York Times* was replaced by the London *Times* the experiments failed to work! It seems hardly worth telling what difference in the manufacture of the paper was really responsible.

In Melbourne I had been completely away from the hospital wards for twenty years but in Boston I found I was expected to have retained clinical interests. One morning, J. H. Means took me around the Massachusetts General Hospital and under the 'Ether dome', beneath which Morton had for the first time given ether as an anaesthetic for a surgical operation just on one hundred years previously, he bade me discourse to the students on a patient with pneumonia. By gently switching the topic to influenza, I got by.

Dr Wesselhoeft likewise took me around the Haynes Memorial Hospital for infectious disease and there I was able to raise enthusiastic interest in one of Australia's greatest medical achievements. Two years previously, Norman Gregg of Sydney had discovered that German measles during pregnancy of the mother could result in congenital cataract and blindness in the child. He published the finding in the relative obscurity of an Australian ophthalmological journal and no one in America had heard of it. Wesselhoeft was greatly impressed, wrote an editorial about the condition for the *New England Journal of Medicine*, and Gregg's discovery had at last come into the full stream of contemporary medicine.

One other clinical experience in Boston was even more unexpected. It happened on my very first night in the Harvard Club on Commonwealth Avenue and here I quote from one of those diary letters:

> 'I was sound asleep when the telephone rang. I got up and heard in a semi-comatose state, a request that I would see a young fellow in No. 47 who appeared to be seriously ill. It took me some time to determine: (a) who was speaking; (b) whether he had meant to ring me; (c) whether he knew I was an Australian and not an American; (d) whether there wasn't any other doctor (a properly qualified American doctor) in the house; and finally, whether he thought my prospective patient really needed to see anyone. The answers were that it was the senior Club attendant, a venerable and intelligent personality; that the patient was a scion of one of the best Boston families (his grandfather had been Ambassador to England); that the only other doctors in the place were elderly and hated to be disturbed and that the boy was probably only nervous and homesick but said he felt very ill and wanted to see a doctor.
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> 'So I agreed to go down with the steward and found a neurotic youngster of eighteen or so with a normal pulse, temperature and facial colour—and a mild tummy upset. So I reassured him, gave him one of my sample sedative tablets and went back wishing that I had the nerve to charge him $10 for a night call. The steward told me he was all right in the morning.'

The Dunham lectures seemed to be successful. I had an interesting story to tell of virus diseases looked at from an ecological angle. It was a topical subject and drew a large audience. I find that I must have paid special attention to the size of the audience because after the third lecture I wrote that all seats had been occupied in each (about 300) and that there were about 50, 70 and 100 standing at the periphery in consecutive lectures. Someone congratulated me on being the first Dunham lecturer for some years whose third lecture was as well attended as his first.

Most of my discussions in America were on matters fairly directly related to the war. At Fort Bragg the Army had a first-rate group working on respiratory diseases with influenza the central but not exclusive interest. There, as at several other centres, I demonstrated how a chick embryo could be inoculated into the amniotic cavity, the only situation in which influenza virus straight from the human patient would grow. Others were interested in that plague of military camps, CSM (cerebrospinal meningitis), and large-scale successful tests were under way to use chemopreventive measures against it. In camps at risk, everyone had a sulphadiazine tablet night and morning for ten days in the hope, usually fulfilled, of getting rid of all carriers. At Ann Arbor I was told how the search for the perfect antimalarial drug was proceeding—chloroquine emerged as the best of the

thousands tested and it was felt to be unfortunate that it had been synthesized by the Germans before 1939. At Yale and Washington, scrub typhus was the major interest. We had worked with it in Melbourne and we had sent the first culture from the New Guinea area to Washington a few months before. Within another year chloramphenicol would be available to deal with scrub typhus, but many servicemen had died by then and the death of Dora Lush from a laboratory infection in our own Institute eight or nine months previously was very much in my mind.

The Allied attack on Italy was in progress at the time and already I was hearing about the success of DDT in handling the explosive typhus situation in Naples. It was a story of exactly the type that Meyer relished and it lost nothing in the telling. The significance of DDT for the control of malaria was also being whispered about. K.F. told me the story of the set of ponds chosen for controlled tests on mosquito larvae. The experimental ponds were rapidly freed but then the larvae vanished also from the *control* (untreated) ponds. The solution? DDT was so powerful that when ducks moved from one of the experimental ponds to the untreated ones they carried enough DDT on their plumage to produce a larvicidal concentration in the water!

I shall always regard the war and the immediate post-war period as the time when the full possibilities of control of infectious disease were realized or could be clearly envisaged. But a new epoch of biological science was also opening and I saw something of its beginnings on that American visit.

On a number of occasions, I have spent longer or shorter times during the summer months at Cold Spring Harbor but I first saw it on New Year's Eve 1943. It was a lovely winter morning when I arrived, the inlet icebound but cracking with the tides, and there were dozens of seagulls lining the cracks or peppered over the ice. Bare woods, brown fields, nice houses and country lanes made me feel that it would be pleasanter to take a long winter walk than to talk about genes and viruses. In fact, I had an unforgettable time with Demerec and his staff. My most vivid recollection is of seeing for the first time how *Drosophila* was handled by geneticists. I had read much of fruit-fly genetics but had never seen the insect itself. So I was introduced to them living in quarter-pint cream bottles with a nutrient mixture of corn meal, molasses and yeast at the bottom—insignificant little flies but at that time the most highly pedigreed animals in the

world. Demerec was at that time a *Drosophila* geneticist. A few years later he moved into bacterial genetics. Signs of the move were only just appearing, perhaps I helped it on. After lunch in the Director's house I gave an informal talk on mutation in influenza virus—the O to D phase change—adopting a genetic approach. I noted at the time that geneticists were just becoming interested in bacteria and bacteriophages. I was assured that the concepts I was developing about influenza virus variation and selection were sound and I came away with the distinct impression that my geneticist audience was delighted to find a microbiologist with a real interest in their science! What a change took place in the next dozen years: by then, most geneticists were bacterial geneticists!

At the Rockefeller Institute I called on O. T. Avery who, in the words of a letter of mine to Linda: 'has just made an extremely exciting discovery which, put rather crudely, is nothing less than the isolation of a pure gene in the form of desoxyribonucleic acid.' I think that must be almost the last time I ever wrote DNA in full. Nothing since has diminished the significance or importance of Avery's work. Neither he nor I knew it at the time but in retrospect the discovery that DNA could transfer genetic information from one pneumococcus to another almost spelt the end of one field of scholarly investigation, medical bacteriology, and heralded the opening of the field of molecular biology which has dominated scholarly thought in biology ever since. Avery was an oldish man then, beginning to live a little in the past, and happy to relate to interested visitors how his work with the pneumococcus had reached this climax. He told the story well and with pride. I feel that Avery's work was so important a link between the old and the new that I should attempt to describe it.

We have almost forgotten that pneumonia was once the 'captain of the men of death' but for the period between the two wars the study of pneumonia and the other pneumococcal infections was the most active and successful area of bacteriological research. The Rockefeller Institute was the world centre for that research and over the whole period Avery was its guiding spirit though he had many brilliant collaborators, Dubos and Heidelberger among them.

The key finding was that the pneumococci could be divided into 'types' in the sense that if a man or an animal became

immune to Type I, he was not thereby immune to Types II, III and so on. Then, around 1920-23, these type differences were found to depend on the fact that the pneumococcus is surrounded by a gummy material, chemically a carbohydrate very like certain vegetable gums, which is vitally important for the disease-producing capacity of the pneumococci, and whose detailed composition varies according to type. This gum was called specific soluble substance SSS, that responsible for Type I was SSS I, for Type III, SSS III and so on. A pneumococcus could live without its SSS but without it, all its pathogenicity was gone. Its appearance in culture also differed from the intact form, so bacteriologists spoke of them as 'rough' or R forms, in contrast to the S or 'smooth' pathogenic varieties. Perhaps the most important point of all to grasp was that when a smooth Type I mutated to a form incapable of producing SSS I, it became a rough pneumococcus which was exactly equivalent to a rough form derived from Type III or any other smooth type. The capacity of the microbe to produce SSS was something that could be pictured as resulting from the addition of a specific piece of genetic mechanism to the mechanism common to all pneumococci. Avery showed that this was not only a useful mode of thought but a physical reality.

The first sign-post on the road was due to an Englishman, Griffiths, in 1928. He was testing whether harmless R pneumococci had any power to immunize mice. For some experiments he injected living R pneumococci whose ancestors had been Type II, along with killed pneumococci of Type III. The mice died but it was Type III pneumococci that were responsible for the death. There was no technical mistake, something from the dead Type III pneumococci had made the living R pneumococci produce, not their lost ancestral SSS II, but the alien SSS III. In 1932, the approach to the problem was considerably simplified. It was found that a soluble extract of Type III could be made to change any R pneumococcus to a virulent Type III and that this could be done in a test-tube. The problem for Avery and his team was now to find what was the substance in the extract which induced the change. On first thought, one might imagine a simple transfer of the SSS itself but that is immediately ruled out by the fact that the changed organisms can multiply indefinitely and in the process *produce* unlimited supplies of the new SSS. That was the crux of the matter, what was transferred was

in a real sense *information* native to Type III which could be transferred as a soluble chemical to any type of R mutant and give it a new inheritance capacity to produce SSS III. By painstaking experiments the active material was isolated. It was DNA. All the control experiments to test the possibility of any mistake came up with the same answer. It was an answer that some biochemists were beginning to expect—the time was propitious for the announcement *that genetic information is carried in the chemical structure of DNA*. That statement remains today as the cornerstone of molecular biology.

Fourteen years later I had dinner in Nashville with Avery's younger brother, Dr Roy Avery, to whom his medals and other memorabilia had been left on his death in 1955. Looking at those medals and thinking of that morning in December 1943, I knew that I could no more forget Avery as a person, than the world can ever forget his work as a scientist.

Across the continent at Cal. Tech. (California Institute of Technology) I called on Beadle and Tatum, again at an almost climacteric moment in the development of the new approach to biology. Their work on the genetics of the bread-mould *Neurospora* had virtually brought them to the famous generalization: 'One gene, one enzyme,' which in slightly more sophisticated form is still the basis of biochemical genetics. The first 'biosynthetic processes' were being worked out and the enormous convenience of micro-organisms for combined genetic and biochemical studies was just being realized. I realized even then how important their work was and I have never forgotten how at that time most of it was being done on makeshift benches in a corridor. It is of the nature of things scientific that really great discoveries are always made with inadequate facilities and amateurish techniques.

The change to molecular biology was on the way but it was relatively insignificant. The war was the important thing and microbiology was predominantly geared to war activities. The last interlude I want to speak of, on the way from Los Angeles back to San Francisco, again had to do with the Armed Services. It was at Bakersfield where Hammon, an epidemiologist from Meyer's Institute, picked me up and took me out to an Air Force establishment on the desert. There, C. E. Smith was handling a research programme on a queer disease, coccidioidomycosis or

laboratory work are as much needed in war as the application of current knowledge' and their 'readiness to make large scale human experiments' whenever this seemed to be needed. From an Australian angle I had to recognize the 'gravitational process by which large centres grow at the expense of smaller ones' and the role of Australia and other outlying countries as 'nurseries from which men of ability could be sent to the major centres to assist there in the effective advance of knowledge'. Having said that, I spent the rest of the lecture giving reasons why we should and could resist what in those days was not yet called the brain drain.

Today much of what I said sounds platitudinous. I am not now so sure as I was that teaching is only effective if it is done by persons actually engaged in research. I would still agree with what I said about the virtues of bringing medical students and young graduates into clinical research as 'normal controls', and about the function of research in a rather limited sense as a channel by which advances from elsewhere are incorporated into hospital practice.

I was still starry-eyed about my Harvard experience and spoke of the reason for Harvard's greatness. 'Subject always to the criticism that I found what I was looking for, I felt certain that the reason was the whole-hearted recognition that medicine today can advance only as a science advances, that the men who teach it must be trained in the methods of scientific investigation and that the senior teachers must have the time and opportunity to keep alight the enthusiasm for research that gained them their present status.'

For Melbourne I wanted something as like Harvard Medical School as circumstances would allow. 'Each of the general teaching hospitals, the Women's Hospital and the Children's Hospital should have one or more clinical units headed by a full-time professor responsible both for the organization of teaching and for the conduct of clinical and associated research in his department.' If this came about it might become appropriate for the Walter and Eliza Hall Institute to work wholly at the fundamental level perhaps with a special relationship to the National Health and Medical Research Council. The Institute in fact moved in this direction while I was its head but the special relationship has only now been achieved by my successor. My next suggestion was based on the importance of paediatric research.

'An institute of child health associated with the Children's Hospital and perhaps under the direction of the professor of paediatrics might well be an early post-war objective.' In due course it came and prospered. I finished by asking how we were to retain first-class men against the gravitational pull to the larger centres overseas. 'The only solution is to provide opportunities in Australia where such men can find full scope for their abilities, where they can feel they are doing work whose value is recognized by the community and where successful work is rewarded by prestige and reasonable financial security.' This was said honestly and in 1944 it was the right and timely thing to say. To some extent it will always be true, provided only that the proportion of men in research does not deplete the limited pool of men of first-rate quality needed for more urgent services to the community, and that the research they are engaged in is such that can be recognized by the community generally as of value and worthy of reward.